UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/419,545	10/18/1999	AYUB DARJI	29473/10277	1400

7590 12/10/2002

MARSHALL O'TOOLE GERSTEIN MURRAY
AND BORUN
6300 SEARS TOWER
233 SOUTH WACKER DRIVE
CHICAGO, IL 606066402

EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 12/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/419,545	Darji et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 18, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-10* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 09/18/02 (paper no. 19) in response to the non-final Office Action mailed 03/29/02 (paper no. 17). With this, Applicants have amended the specification.

Status of Claims

2) Claims 1, 4 and 6 have been amended via the amendment filed 09/18/02.

Claims 1-10 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Maintained

5) The objection to the abstract made in paragraph 8 of the Office Action mailed 03/29/02 (paper no. 17) is maintained for reasons set forth therein and herebelow. The abstract still improperly contains two separate paragraphs as opposed to one and further contains more than 150 words. See MPEP § 608.01(b).

6) The objection to the specification made in paragraph 9(i) of the Office Action mailed 03/29/02 (paper no. 17) is maintained for reasons set forth therein and herebelow. Essential headings/sections such as 'Summary of the Invention'; 'Brief Description of the Drawings'; 'Detailed Description of the Invention' etc. are still missing.

Objection(s) Withdrawn

7) The objection to the drawings made in paragraph 5 of the Office Action mailed 03/29/02 (paper no. 17) under 37 CFR 1.84 is withdrawn in light of Applicants' submission of formal drawings on 09/18/02 (paper no. 19). These drawings have been approved by the Draftsperson.

8) The objection to the specification made in paragraph 9(ii) of the Office Action mailed 03/29/02 (paper no. 17) is withdrawn in light of Applicants' amendments to the specification.

9) The objection to the specification made in paragraph 9(iii) of the Office Action mailed 03/29/02 (paper no. 17) is withdrawn in light of Applicants' amendments to the specification.

10) The objection to the specification made in paragraph 9(iv) of the Office Action mailed 03/29/02 (paper no. 17) is withdrawn in light of Applicants' amendments to the specification.

11) The objection to claims 4 and 5 made in paragraph 14(b) of the Office Action mailed 03/29/02 (paper no. 17) is withdrawn in light of Applicants' amendments to the claims.

12) The objection to claims 1 and 6 made in paragraph 14(c) of the Office Action mailed 03/29/02 (paper no. 17) is withdrawn in light of Applicants' amendments to the claims.

Objection(s) Maintained

13) The objection to the specification made in paragraph 9(v) of the Office Action mailed 03/29/02 (paper no. 17) is maintained for reasons set forth therein.

14) The objection to the specification made in paragraph 9(vi) of the Office Action mailed 03/29/02 (paper no. 17) is maintained for reasons set forth therein.

15) The objection to the specification made in paragraph 9(vii) of the Office Action mailed 03/29/02 (paper no. 17) is maintained for reasons set forth therein.

16) The objection to claim 1 made in paragraph 14(a) of the Office Action mailed 03/29/02 (paper no. 17) is maintained for reasons set forth therein.

17) The objection to claim 9 made in paragraph 14(d) of the Office Action mailed 03/29/02 (paper no. 17) is maintained for reasons set forth therein.

Specification

18) The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R 1.75(d)(1) and MPEP § 608.01(o). Claim 6, as amended, recites the limitation: "cytomegalovirus". However, there appears to be no antecedent basis for this recitation in the specification, as originally filed.

Rejection(s) Withdrawn

19) The rejection of claim 7 made in paragraph 13(a) of the Office Action mailed 03/29/02

(paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn.

20) The rejection of claim 6 made in paragraph 13(b) of the Office Action mailed 03/29/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants's amendment to the claim.

21) The rejection of claim 6 made in paragraph 13(e) of the Office Action mailed 03/29/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants's amendment to the claim.

22) The rejection of claim 3 made in paragraph 10 of the Office Action mailed 03/29/02 (paper no. 17) under 35 U.S.C § 112, first paragraph, as failing to provide an enabling disclosure, with regard to the deposit issue, is withdrawn.

Rejection(s) Maintained

23) The rejection of claim 1 made in paragraph 13(a) of the Office Action mailed 03/29/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and herebelow.

Applicants contend that minute fractions of a gene would be less desirable to use than larger fragments and that minute fragments are within an open reading frame. Applicants further state that claim 7 properly avoids a size or length limitation relating to the gene fragment.

Applicants' arguments have been carefully considered, but are non-persuasive. The rejection under 35 U.S.C § 112, second paragraph, that remains is for claim 1, not for claim 7. The limitations in claim 7 do not address the rejection directed to the independent claim 1. It is still unclear what is encompassed in the recitation "fragment" in claim 1, or what characteristics and/or length a gene should have in order to qualify as a 'fragment'. Does a single or double nucleotide base(s) of a heterologous or autologous gene qualify as a fragment?

24) The rejection of claim 9 made in paragraph 13(c) of the Office Action mailed 03/29/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and herebelow.

Applicants contend that the term 'variant' is known in the art to refer to a variation of a wild-type gene sequence and that variations include truncated variants and mutated variants.

Applicants' arguments have been carefully considered, but are non-persuasive. The term 'truncated variant' is vague and indefinite because it is unclear what part of the gene is truncated, or what length of the gene is truncated in the variant. The metes and bound of the 'truncated variant' is indeterminate since it is not clear what does this variant encompass structurally.

25) The rejection of claim 8 made in paragraph 13(c) of the Office Action mailed 03/29/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

26) The rejection of claims 2-9 made in paragraph 13(f) of the Office Action mailed 03/29/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

27) The rejection of claims 1-10 made in paragraph 11 of the Office Action mailed 03/29/02 (paper no. 17) under 35 U.S.C § 112, first paragraph, with regard to the scope, is maintained for reasons set forth therein and herebelow.

Applicants contend that claims 1-9 are to an attenuated *Salmonella* strain comprising a eukaryotic expression vector for the expression of a heterologous gene or heterologous gene fragment or an autologous gene or autologous gene fragment comprised within an open reading frame. Applicants acknowledge that attenuated strains of *Salmonella* suitable for vaccination were known in the art. Applicants also admit that expression vectors comprising a heterologous gene or heterologous gene fragment or an autologous gene or autologous gene fragment comprised within an open reading frame were known in the art. Applicants further state that although known in the art as a 'routine' procedure, introduction of an expression vector into *Salmonella* was described in the specification along with a great number of uses for the claimed *Salmonella* strains. Applicants point to pages 8-10 of the specification and state that one such use is the "introduction of the expression product into a mammalian cell by contacting the cell with a claimed Salmonella strain for expression of a heterologous gene or heterologous gene fragment or an autologous gene or autologous gene fragment within the mammalian cell". With this, Applicants conclude that the specification teaches one of ordinary skill in the art how to make and use the invention of claims 1-9. Applicants correctly note the Office's noticing of at

least one of the purposes of the invention to be vaccination, yet allege that the Office focuses on the heterologous gene fragment or the autologous gene fragment. Applicants assert that the pending claims are drawn to a "vehicle" [Emphasis in original], but not to a coding region for an immunogenic polypeptide. Applicants submit that a claimed automobile for carrying passengers does not fail for lack of enablement because the specification fails to specifically identify the passengers. Applicants assert that coding regions for peptides whose immunogenicity is unknown could be identified using the type of routine experimentation found acceptable in *In re Wands*. Applicants further assert that with the enablement inquiry properly focused on the claimed vehicle, the full scope of claims '1-10' is enabled by the specification.

Applicants' arguments have been carefully considered, but are non-persuasive. The instant claims are not drawn to a method of a great number of uses for the *Salmonella* strains, which Applicants acknowledge are routinely known in the art. The claims are not directed to a method of introducing an expression product into a mammalian cell either. Instead, the claims are drawn to an attenuated non-mammalian *Salmonella* strain comprising a eukaryotic expression vector which vector comprises a heterologous or autologous gene or a fragment thereof. As set forth in paragraph 11 of the Office Action mailed 03/29/02, while the specification is enabling for an attenuated *Salmonella* strain comprising a eukaryotic expression vector for expressing a heterologous gene wherein said vector 'comprises' said heterologous gene within an open reading frame and expresses an *E. coli* beta-galactosidase, *Listeria monocytogenes* listeriolysin, or *Listeria monocytogenes* ActA protein, does not reasonably provide enablement for an attenuated *Salmonella* strain wherein an autologous gene or a fragment thereof, or a fragment of a heterologous gene is comprised within the vector and expressed, wherein the strain is suitable for vaccination of vertebrates, as claimed. Furthermore, other than the specific listeriolysin variant and ActA variant described in the first paragraph on page 5 of the specification, the instant disclosure does not reasonably provide enablement for an attenuated *Salmonella* vaccine strain expressing any other truncated variant of a *Listeria monocytogenes* listeriolysin or any other truncated variant of a *Listeria monocytogenes* ActA protein, as claimed broadly. Applicants' analogy to an automobile "for carrying passengers" is misplaced, since what is currently claimed is not a mere *Salmonella* strain "for carrying" a heterologous gene, heterologous gene fragment,

autologous gene or autologous gene fragment. Instead, the claims are directed to an attenuated *Salmonella* strain "comprising" a eukaryotic vector for the expression of a heterologous gene, heterologous gene fragment, autologous gene or autologous gene fragment which fragment is necessarily "comprised by the vector". Thus, contrary to Applicants' assertion, a fragment of a coding region is required to be comprised or incorporated in the expression vector that is contained in the claimed strain. For one to incorporate such a gene fragment, one need to know what exactly it contains or encompasses. Claims 1-9 are drawn to a *Salmonella* strain comprising a 'gene fragment'. Claims 1-6, 8 and 9 are not drawn to a vaccine. The precise size and/or structural composition of the 'gene fragment' comprised within the vector of the *Salmonella* strain is not disclosed. It should be noted that a single nucleotide base constitutes a gene fragment and is encompassed in the fragment recited, for example, in claim 1. As written currently, claim 1 does not exclude fragments comprising one or two nucleotides. There is no description in the instant specification that guides one of skill in the art as to which fragment from which part of a heterologous or autologous gene (i.e., central or terminal parts, or both) could be chosen for inclusion in the claimed *Salmonella* strain such that the strain is of some utility, either as a vaccine for vertebrates, or as a diagnostic reagent.

With regard to claim 8, as set forth in paragraph 11 of the Office Action mailed 03/29/02, there is lack of disclosure as to the precise disease (infectious or non-infectious) or the clinical condition, which the recited antigen is allegedly "protective" against. It is noted that Applicants have not addressed the issue raised by the Office with regard to the *prima facie* evidence within the instant specification, i.e., the failure of a *S. typhimurium aroA* strain carrying a eukaryotic expression plasmid, pCMVactA, encoding amino acids 31-613 of the ActA protein of *Listeria monocytogenes,* to induce a protective immune response (see paragraph bridging pages 16 and 17; and Figure 4).

With regard to the broad recitation of truncated variants in claim 9, a *Salmonella* strain expressing a myriad of truncated variants of listeriolysin or truncated variants of actA protein of *Listeria monocytogens*, is encompassed in the scope of the claim. However, the only truncated and non-hemolytic variant of listeriolysin that is enabled or shown to be expressed via the claimed *Salmonella* strain is a variant that consists of amino acids between positions 26-482. Similarly,

the only truncated variant of ActA membrane protein that is enabled or shown to be expressed via the claimed *Salmonella* strain is a variant that consists of amino acids between positions 31-613 (see page 5). While the former strain expressing said listeriolysin variant was demonstrated to be a protective vaccine against challenge with *Listeria monocytogenes*, the latter strain expressing said ActA variant was shown to be a **non**-protective vaccine against challenge with *Listeria monocytogenes*. See Figure 4. Even the truncated variant of ActA membrane protein when expressed via the claimed *Salmonella* strain did not prove to be a suitable (protective) vaccine for vertebrates against listeriosis (see Figure 4). This is critical, because the expression of a truncated bacterial polypeptide by truncating any of part the gene responsible for its expression such that it retains its three dimensional conformation and remains functionally and/or biologically active, is not a predictable event. Therefore, it is not predictable that any other randomly truncated variant of ActA, if expressed via the claimed *Salmonella* strain, would prove to be "suitable for vaccination of vertebrates". Similarly, if one produced any other truncated variants of listeriolysin other than that described on page 5, first paragraph, and expressed it via the attenuated *Salmonella* strain, it is not predictable that such a strain would serve as an effective vaccine in vertebrates against listeriosis or any other non-specific disease. It is not predictable that the resultant truncated listeriolysin variant would loose the haemolytic activity and retain the functional integrity or biological/immunogenic competence of the native listeriolysin. As set forth in paragraph 11 of the Office Action mailed 03/29/02, the state of the art at the time clearly showed that a mutation or genetic variation at any random position of a wild-type bacterial polypeptide, pneumolysin, which shows sequence homology with listeriolysin, does not always result in a modified pneumolysin polypeptide having an attenuated hemolytic activity. For example, Mengaud *et al.* (*Infect. Immun.* 56: 766-772, 1988 - Applicants' IDS) taught the existence of homologies between the ORF of listeriolysin and pneumolysin (see page 766). Feldman *et al.* (*Am. J. Respir. Cell Mol. Biol.* 5: 416-423, 1991, already of record) showed that, while a Trp 433 > Phe modification resulted in a modified pneumolysin having a lowered haemolytic activity, a Tyr 384 > Phe modification resulted in a modified pneumolysin that had normal hemolytic activity (see page 417). Mitchell *et al.* (*Mol. Microbiol.* 5: 1883-1888, 1991, already of record) showed that individual modifications of Trp 379 and Trp 397 to Phe, or of

residues Tyr 384 and Asp 385 to Phe and Asn respectively, did not alter the cytolytic activities of resultant modified pneumolysins (see page 1885, left column). Similarly, Bowie *et al.* (*Science*, 247: 1306-1310, 1990, already of record) taught that while it is known that many amino acid variations or substitutions are possible in any given protein, the position within the protein's sequence where such amino acid variations or substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). Clearly, the breadth of the instant claim is not commensurate in scope with the disclosure and/or evidence and clearly, one skilled in the art cannot make and use the invention commensurate in scope with the claims without undue experimentation. It is noted that Applicants have also not addressed this issue.

As set forth in paragraph 11 of the Office Action mailed 03/29/02, although a microbial polypeptide or protein when expressed via an attenuated bacterial strain is expected by those skilled in the art to generally induce specific antibodies, the ability of a "truncated variant" of such a polypeptide to serve as an effective vaccine "suitable for vaccination of vertebrates" when similarly expressed, is not certain. The instant specification fails to teach how to express any other "truncated variant" of listeriolysin, or ActA membrane protein such that the bacterial strain expressing the same is capable of serving as a vaccine "suitable for vaccination of vertebrates". The specification provides no guidance as to which specific amino acids may be truncated or varied without causing any detrimental effect to the polypeptide which is to be expressed via the *Salmonella* strain meant for use as a vaccine in vertebrates. There is no disclosure in the instant specification with regard to which other amino acid variations, i.e., truncations, in listeriolysin or ActA membrane protein, would result in a ActA "variant" or a non-hemolytic listeriolysin "variant" that would be immunogenically and biologically functional as the native polypeptide. This is important because the art reflects unpredictability as to which amino acids in a specific polypeptide can be varied, i.e., replaced or added, without adversely affecting the functional properties of that specific polypeptide. While it is known in the art that truncation or variation in one or more amino acids is possible in a given bacterial polypeptide, the exact position within its amino acid sequence where truncations or variations can be made, with a reasonable expectation

of success of retaining the polypeptide's functional integrity, is not certain. A random truncation affecting the epitopic amino acid positions that are critical, for example, to the three-dimensional conformational structure and specific binding or protective property of the protein, would result in a polypeptide that may be non-functional (i.e., non-immunogenic or non-protective) or not optimally immunogenic or protective as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986, already of record) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool.

Thus, the art reflects that variations in critical residues at specific positions in an amino acid sequence could result in a polypeptide which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. In the instant case, this is important because at least one of the purposes of the instant invention is to produce a *Salmonella* strain expressing a heterologous polypeptide or protein that is "suitable for vaccination of vertebrates" as recited in claim 1, or wherein the expressed polypeptide serves as a "protective antigen" as recited in claim 8. It is noted that Applicants have not addressed this issue.

In view of the recognized unpredictability of expressing a truncated bacterial polypeptide via a recombinant bacterium which polypeptide retains its three dimensional structure and biologic, protective and/or immunogenic functions by truncating any part of its gene, Applicants' own evidence showing that the *Salmonella* strain expressing a specific truncated variant of the ActA membrane protein proved to be a non-protective vaccine against challenge with *Listeria monocytogenes*, the art-demonstrated unpredictability in determining amino acid variations that result in non-hemolytic variants of listeriolysin, the lack of disclosure and working examples enabling the full scope, the quantity of experimentation necessary and the breadth of the claims, undue experimentation would have been required by one of ordinary skill in the art to

reproducibly practice the full scope of the invention as claimed. One of ordinary skill in the art would not be able to make and use the claimed *Salmonella* strain, for example, as a vaccine, without undue experimentation, because there is no disclosure as to what positions and what specific amino acid residues are embraced by the "fragment" or "variant" recited in the instant claims. The production and use of the claimed *Salmonella* strain that is capable of serving as a suitable vaccine for vertebrates is well outside the realm of routine experimentation. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 102

28) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> **(e)** The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

29) Claims 1-4, 7, 8 and 10 are rejected under 35 U.S.C § 102(e) as being anticipated by Curtiss III *et al.* (US 5,656,488).

Curtiss III *et al.* disclosed an attenuated strain of *Salmonella typhimurium* or *Salmonella typhi* comprising a recombinant expression vector expressing a heterologous eukaryotic gene encoding human LDH-C or gamete-specific antigen SP-10 wherein the attenuated strain is suitable for vaccination of vertebrates. See abstract; Examples 5, 6, 9 and 10; claims; Table 1; and 'Commercial Utility'. The strain of *Salmonella typhimurium* that can be used is LT2 (see Table 1, under section B). The LDH-C or SP-10 polypeptide expressed by the attenuated strain elicited immunogenic response in a subject (see first three lines in first and third full paragraphs in column 2; section A in Example 9; and section 5 under Example 10).

Claims 1-4, 7, 8 and 10 are anticipated by Curtiss III *et al.*

30) Claims 1, 2, 7, 8 and 10 are rejected under 35 U.S.C § 102(b) as being anticipated by Srinivasan *et al.* (*Biol. Reproduct.* 53: 462-471, 1995).

Srinivasan *et al.* taught a recombinant, attenuated *Salmonella typhimurium* strain

comprising a delivery vector comprising a heterologous eukaryotic gene that expresses an immunogenic human sperm antigen SP10 and an a vaccine comprising the same. Mice immunized with the attenuated recombinant *Salmonella typhimurium* developed sperm-specific antibodies (see title; abstract; Materials and Methods; and Results).

Claims 1, 2, 7, 8 and 10 are anticipated by Srinivasan *et al.*

Rejection(s) under 35 U.S.C. § 103

31) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

32) Claims 1, 5, 6 and 9 are rejected under 35 U.S.C § 103(a) as being unpatentable over Curtiss III *et al.* (US 5,656,488) in view of Rock (US 5,869,057), Vogelstein *et al.* (US 6,054,570) or Chada *et al.* (US 5,736,388).

The references of Curtiss III *et al.*, Rock, Vogelstein *et al.* and Chada *et al.* are applied in this rejection because they qualify as prior art under subsection (e) of 35 U.S.C § 102 and accordingly are not disqualified under U.S.C 103(a).

The teachings of Curtiss III *et al.* are explained above, which do not disclose their *Salmonella typhi* strain to be Ty21a, or the heterologous gene to be the *E. coli* beta-galactosidase gene.

However, the specific and conventional use of Ty21a strain of *Salmonella typhi* to express

foreign proteins and the inclusion of the pCMV-beta-gal expression vector in a recombinant strain were well known in the art at the time of the instant invention. For example, Rock taught the use of an attenuated strain of *Salmonella typhi*, Ty21a, or an attenuated aroA *Salmonella typhimurium* for carrying a heterologous eukaryotic gene specifying a foreign antigen that induces antibodies (see section 2.3.6 Salmonella). The expression operon that is inserted is the beta-galactosidase gene (see second full paragraph in column 21). Vogelstein *et al.* or Chada *et al.* taught the conventional use of the commercially available plasmid expression vector pCMV-beta-gal. See paragraph bridging columns 5 and 6 of Vogelstein *et al.* and first full paragraph in column 36 of Chada *et al.*

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use Rock's attenuated strain of *Salmonella typhi*, Ty21a, in place of Curtiss's generic *S. typhi* strain, or incorporate Chada's or Vogelstein's pCMV-beta-gal into Curtiss's attenuated *Salmonella* strain to produce the instant invention, with a reasonable expectation of success, since Rock taught that it was conventional to use *Salmonella typhi*, Ty21a, to express a foreign gene, or since Vogelstein *et al.* or Chada *et al.* taught that recombinant incorporation of pCMV-beta-gal was conventional during a protein expression. Substitution of one strain with another, specific, art-known strain or the insertion of an art-disclosed heterologous gene and incorporation of an art-known expression vector into an art-known strain would have been well within the realm of routine experimentation and would have been obvious to one of skill in the art, absent evidence to the contrary.

Claims 1, 5, 6 and 9 are *prima facie* obvious over the prior art of record.

Prior Art

33) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Rock (US 5,869,057) taught recombinant *E. coli* harboring eukaryotic CTP expression vector expressing the heterologous, eukaryotic immunogenic CTP antigen and recombinant vaccines that induces antibodies against a self protein for use in immunological prophylaxis and therapy in mammals, and an attenuated aroA *Salmonella typhimurium* for

carrying a heterologous eukaryotic gene specifying a foreign antigen. The self protein is the carboxyl terminal peptide (CTP) of human chorionic gonadotropin (hCG) (see abstract; section 2.3.6 Salmonella; third full paragraph in column 13; second full paragraph in column 21) are taught (see section 7.3; and column 22, lines 13 and 14; and third full paragraph in column 22).

- Brown *et al.* (*J. Infect. Dis.* 155: 86-92, 1987) taught an attenuated aroA *S. typhimurium* vaccine strain expressing a cloned b-galactosidase (see abstract).

- Pestka (US 5,986,061, filed 1988) disclosed host microorganisms transformed with expression vectors containing heterologous eukaryotic genes encoding human interferon proteins. Other microbial strains that can be used as host cells for transformation include *Salmonella typhimurium*. Various plasmids, expression vectors and promoter systems that can be used are taught (see abstract; and column 27, lines 34-55).

- Goeddel *et al.* (US 5,231,176) disclosed a microorganism transfected with an expression vector harboring a suitable promoter and a heterologous eukaryotic DNA molecule that encodes a human leukocyte interferon. Microorganisms that can be used for transfection include *Salmonella* (see claims; paragraph bridging column 3 and 4; and first full paragraph in column 4).

- Carr (US 6,365,576) discloses that plasmid pCMV-beta, a eukaryotic expression vector, is purchased from Clontech Laboratories, Inc., Palo Alto, California and that it contains an *E. coli* beta-galactosidase reporter gene under the control of the human cytomegalovirus (CMV) immediate early promoter/enhancer, an RNA splice donor and acceptor sequence, and the SV40 late polyadenylation signal. The CMV promoter is described as a systemically-expressed promoter which causes expression only in the tissue of interest (see last paragraph in column 3).

Remarks

34) Claims 1-10 stand rejected.

35) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone

number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

36) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

December, 2002

SD
S. DEVI, PH.D.
PRIMARY EXAMINER